

First Morning Voided Urinary Gonadotropin Measurements for the Early Screening, Diagnosis and Follow-up of Central Precocious Puberty Patients

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Table 1. Schedule of study procedures

Study Day/Week:	CPP patients (diagnosis and treatment time)				
	Week 0/ Day 1/first diagnose	Week 12	Week 24	Week 36	Week 48
Visit Windows (Days):	NA	±5d	±5d	±5d	±5d
Visit Number:	1	2	3	4	5
Informed consent	X				
Inclusion/exclusion criteria	X				
Demographics and medical history	X				
Medication history	X				
Physical examination	X	X	X	X	X
Vital signs	X	X	X	X	X
Weight and height	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Concurrent medical conditions	X				
Predicted adult height	X		X		X
Tanner staging evaluation	X	X	X	X	X
Bone age	X		X		X
FMV urinary Gn	X	X	X	X	X
Adrenal axis evaluation	X				
Hematology, urine analysis, clinical chemistry, glucose, insulin	X		X		X
ECG	X				
Adrenal b-ultrasound	X				
Pelvic/Testicular ultrasonography	X		X		X
LH and FSH	X	X	X	X	X
Estradiol or Testosterone	X	X	X	X	X
Stimulation test (GnRH)	X				
Cranial MRI	X				
CEA, AFP, β-HCG	X				
Injection investigational drug	X	X	X	X	X
PTE assessment	X				
AE assessment	X	X	X	X	X

References

- Zhu M, Fu J, Liang L, et al. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2013 Jul;42(4):396-402. Chinese.
- Latronico AC, Brito VN, Carel JC. Lancet Diabetes Endocrinol. 2016 Mar;4(3):265-274.
- Lucaccioni L, McNeilly J, Mason A, et al. Hormones (Athens). 2016 Jul;15(3):377-384.
- Kolby N, Busch AS, Aksglaede L, et al. J Clin Endocrinol Metab. 2017 Oct 1;102(10):3830-3838.
- Demir A, Voutilainen R, Stenman UH, et al. Horm Res Paediatr. 2016;85(5):301-8.
- The Subspecialty Group of Endocrinological, Hereditary and Metabolic Disease, the Society of Pediatrics, Chinese Medical Association, Editorial board of the Chinese journal of pediatrics. Zhonghua Er Ke Za Zhi. 2015;53(6):412-418.

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Introduction

Central precocious puberty (CPP) is one of the most common pediatric endocrine diseases with an ever-increasing incidence [1]. CPP is associated with the loss of final adult height, early menarche, psychological problems and an increased risk of developing diseases in later adulthood such as female reproductive system tumors [2].

The gonadotropin-releasing hormone (GnRH) stimulation test (GnRHST) is the gold standard for the diagnosis of CPP. However, the test is costly and time consuming to implement because the invasive method requires hospitalization and repeated evaluation with multiple serum sample collections, thus making the test not suitable for routine screening [2].

Recent studies have demonstrated that the first morning voided (FMV) urinary Gn (U-Gn) has a strong correlation with serum Gn (S-Gn) and performed equally well in predicting a pubertal GnRHST [3, 4]. It also performed equally well as the GnRHST in the differentiation of early puberty (Tanner stage 2) from prepuberty (Tanner stage 1) and decreased after 3 months of GnRH analogs (GnRHa) treatment to levels below +2 SDs [5]. Thus, the non-invasive FMV U-Gn measurement can reflect the gonadotropin secretion for a particular period during the day and suggest higher accordance with GnRHST compared with S-Gn, which suggests that FMV U-Gn may be an ideal indicator for CPP screening, diagnosis and follow-up. However, a uniform standard has not been agreed due to the lack of large cohort, multi-center clinical research data. Therefore, it is of great clinical value and scientific significance to study further FMV U-Gn concentration changes and cut-off values.

Objective

The study was designed to explore a reasonable cut-off value of FMV urinary Gn for:

- large-population CPP screening in China
- CPP diagnosis in China
- CPP follow-up in China

Methods

➢ Study design and setting

This is a multi-center, prospective, and randomized controlled study to be conducted in 11 centers in China. This study will be divided into three parts (Figure 1 and Table 1):

Part 1: Approximately 6,000 healthy children will be enrolled and classified at different Tanner stages;

Part 2: About 400 precocious puberty (PP) patients randomly selected from out-patient department will be enrolled and divided into CPP and non-CPP groups according to the results of GnRHST;

Part 3: CPP subjects who received the treatment of GnRHa (3.75 mg, every 4 weeks) will be followed up once every 3 months to measure FMV U-Gn, until the end of the study (1 year).

➢ Participants

The inclusion criterion for healthy pediatric population was aged 6 to 12 years old, without CPP, hepatopathy, nephropathy, congenital heart disease, and hereditary metabolic diseases.

PP group's inclusion criterion is the appearance of secondary sexual characteristics before the age of 8 for girls and 9 for boys. Patients with peripheral PP due to tumors, exogenous factors, congenital adrenal hyperplasia, and McCune-Albright syndrome, hepatopathy, nephropathy, congenital heart disease, and hereditary metabolic diseases will be excluded.

The diagnosis for CPP used in this study will follow the consensus on diagnosis and treatment in 2015 [6].

➢ Planned outcomes

Part 1: Determine the ideal cut-off value of FMV U-LH, U-FSH and U-LH/U-FSH as a screening indicator for clinically established puberty;

Part 2: Determine the ideal cut-off value of FMV U-LH, U-FSH and U-LH/U-FSH as a diagnostic indicator for CPP;

Part 3: Determine the ideal cut-off value of FMV U-LH, U-FSH and U-LH/U-FSH for evaluating the efficacy of clinical treatment.

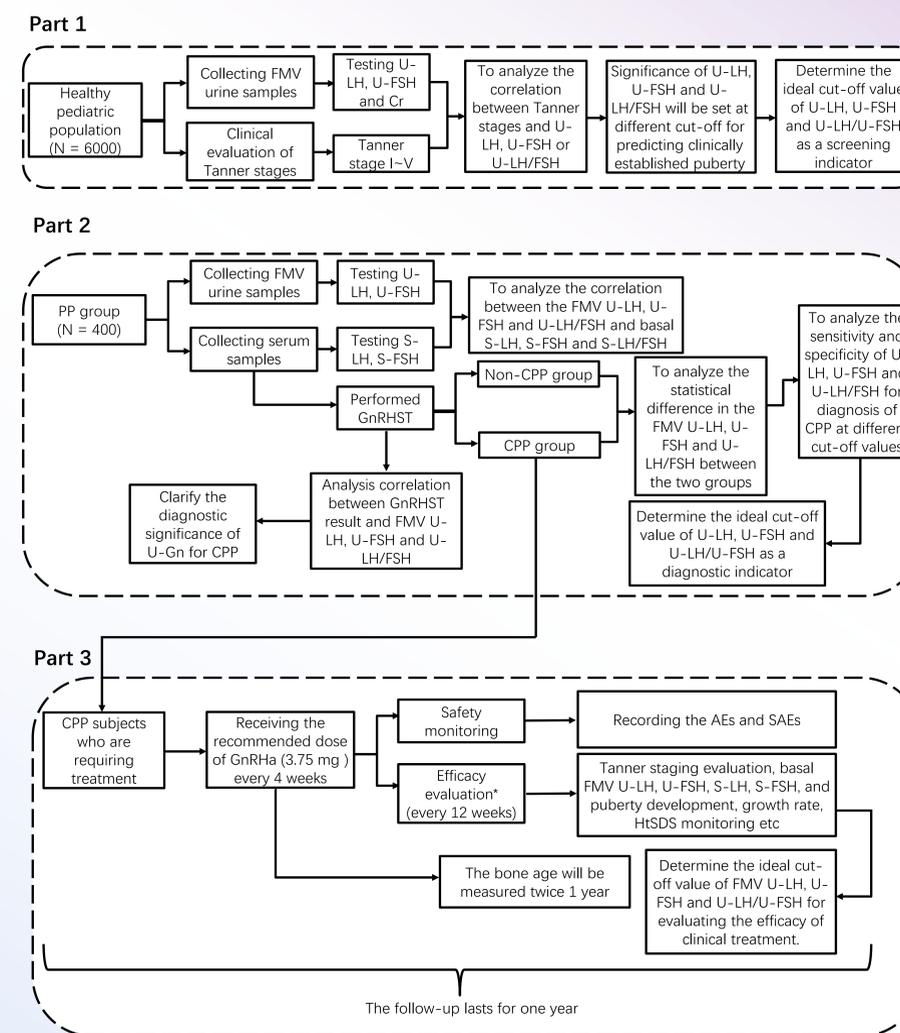


Figure 1. Overview of study design

Conclusion

In this study, we will separately explore the reasonable cut-off values for CPP screening, diagnosis and follow-up through a large-sample, multi-center prospective study in China.